

**BOX PATENT
APPLICATION**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Jasper Rine and Matthew Attorney Docket No.: UOCB118456
Ashby

Title: SYSTEMS FOR GENERATING AND ANALYZING
STIMULUS-RESPONSE OUTPUT SIGNAL MATRICES

PRELIMINARY AMENDMENT

Seattle, Washington 98101

TO THE COMMISSIONER FOR PATENTS:

In the Specification:

Please delete lines 6-8 of the application.

Please revise the section beginning on page 1, before line 10, to add a new section with the heading as follows:

CROSS-REFERENCES TO RELATED APPLICATIONS

The present application is a continuation of pending U.S. Patent Application No. 09/294,453, filed 4/19/99; which is a continuation of U.S. Patent Application No. 08/986,650, filed 12/8/97, now Patent No. 6,326,140, which is a continuation of U.S. Patent Application No. 08/512,753, filed 8/9/95, now Patent No. 5,777,888, priority from the filing dates of which is hereby claimed under 35 U.S.C. § 120.

In the Claims:

Please cancel Claims 1-37 and add new Claims 38-85 as follows:

38 (New) A method for analyzing the effects of subjecting a living thing to a stimulus comprising:

(a) detecting physical signals from a plurality of units ordered in a probe matrix by contacting the probe matrix with gene transcripts or cDNA derived from said living thing subjected to said stimulus, wherein each unit of the probe matrix confines a probe comprising a different pre-determined sequence of nucleotides, and wherein said sequence is hybridizable with an identified gene of said living thing, or with a transcript of the gene, or with cDNA derived from the gene,

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(b) transducing the physical signals into electrical output signals,

(c) storing in digital form each electrical output signal in an output signal data structure, wherein each stored digital signal is associated (i) with said stimulus and (ii) with the identity of said identified gene, and

(d) analyzing the effect of said stimulus on said living thing by comparing the stored output signal data structure with an output signal data structure database, wherein the output signal data structure database comprises a plurality of output signal data structures stored in a computer memory.

39. (New) The method of claim 38 wherein the probes are 24-240 nucleotides in length.

40. (New) The method of claim 38 wherein the probes comprise lengths of nucleotide sequences selected so as to be hybridizable with a transcript or cDNA derived from said identified gene.

41. (New) The method of claim 38 wherein the probes comprise polynucleotide sequences not hybridizable to more than one contiguous gene of the living thing.

42. (New) The method of claim 38 wherein the gene transcripts or cDNA derived from the living thing are labeled.

43. (New) The method of claim 38 wherein the ordered units in a probe matrix comprise an ordered array of units identified by X and Y coordinates, and wherein output signal data structures comprise matrices with elements identified by the X and Y coordinates.

44. (New) The method of claim 43 further comprising establishing a table relating the X and Y coordinates of each unit to the identity of said identified gene.

45. (New) The method of claim 38 wherein the step of storing further comprises storing each digital signal in a computer readable memory.

46. (New) The method of claim 38 wherein the probe matrix comprises oligonucleotide probes that are arrayed on a substrate.

47. (New) The method of claim 38 further comprising a step of producing the output signal data structure database by a method comprising:

- (a) detecting physical signals from a plurality of units ordered in a probe matrix by contacting the probe matrix with gene transcripts or cDNA derived from said living thing subjected to a stimulus, wherein each unit of the probe matrix confines a probe comprising a different pre-determined sequence of nucleotides, and wherein said sequence is hybridizable with an identified gene of said living thing, or with a transcript of the gene, or with cDNA derived from the gene,
- (b) transducing the physical signals into electrical output signals,
- (c) storing in digital form each electrical output signal in an output signal data structure, wherein each stored digital signal is associated (i) with said stimulus and (ii) with the identity of said identified gene, and
- (d) repeating steps of detecting, transducing, and storing for a plurality of stimuli to form an output signal data structure database.

48. (New) The method of claim 47 wherein the probes comprise polynucleotide sequences not hybridizable to more than one contiguous gene of the living thing.

49. (New) The method of claim 38 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 0.5% of the genes of said living thing, or with transcripts of at least 0.5% of said genes, or with the cDNA derived from at least 0.5% of said genes.

50. (New) The method of claim 49 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 5% of the genes of said living thing, or with transcripts of at least 5% of said genes, or with the cDNA derived from at least 5% of said genes.

51. (New) The method of claim 50 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 50% of the genes of said living thing, or with transcripts of at least 50% of said genes, or with the cDNA derived from at least 50% of said genes.

52. (New) The method of claim 38 wherein the probe matrix comprises probes having sequences that are hybridizable with a functional class or subset of the genes of said living thing, or with transcripts of the functional class or subset of said genes, or with the cDNA derived from the functional class or subset of said genes.

53. (New) The method of claim 49, 50 or 51 wherein the living thing is a human.

54. (New) The method of claim 49, 50 or 51 wherein the living thing is a fungus.

55. (New) The method of claim 49, 50 or 51 wherein the living thing is a eukaryote.

56. (New) A method for producing an output signal data structure database recording the effect of subjecting a living thing to a plurality of stimuli comprising:

(a) detecting physical signals from a plurality of units ordered in a probe matrix by contacting the probe matrix with gene transcripts or cDNA derived from said living thing subjected to said stimulus, wherein each unit of the probe matrix confines a probe comprising a different pre-determined sequence of nucleotides, and wherein said sequence is hybridizable with an identified gene of said living thing, or with a transcript of the gene, or with cDNA derived from the gene,

(b) transducing the physical signals into electrical output signals,

(c) storing in digital form each electrical output signal in an output signal data structure, wherein each stored digital signal is associated (i) with said stimulus and (ii) with the identity of said identified gene, and

(d) repeating steps of detecting, transducing, and storing for a plurality of stimuli to form an output signal data structure database.

57. (New) The method of claim 56 wherein the stimuli comprise basal conditions.

58. (New) The method of claim 56 wherein the probes are 24-240 nucleotides in length.

59. (New) The method of claim 56 wherein the probes comprise nucleotide sequences selected so as to be hybridizable with a transcript of or with cDNA derived from identified genes.

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60. (New) The method of claim 56 wherein the gene transcripts or cDNA derived from the living thing are labeled.

61. (New) The method of claim 56 wherein the polynucleotide sequence of each probe is not hybridizable to more than one contiguous gene of the living thing.

62. (New) The method of claim 56 wherein the ordered units in a probe matrix comprise an ordered array of units identified by X and Y coordinates, and wherein output signal data structures comprise matrices with elements identified by the X and Y coordinates.

63. (New) The method of claim 56 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 0.5% of the genes of said living thing, or with transcripts of at least 0.5% of said genes, or with the cDNA derived from at least 0.5% of said genes.

64. (New) The method of claim 63 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 5% of the genes of said living thing, or with transcripts of at least 5% of said genes, or with the cDNA derived from at least 5% of said genes.

65. (New) The method of claim 64 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 50% of the genes of said living thing, or with transcripts of at least 50% of said genes, or with the cDNA derived from at least 50% of said genes.

66. (New) The method of claim 63, 64 or 65 wherein the living thing is a human.

67. (New) The method of claim ~~64~~, 64 or 65 wherein the living thing is a fungus.

68. (New) The method of claim ~~64~~, 64 or 65 wherein the living thing is a eukaryote.

69. (New) A computer memory storing an output signal data structure database produced by the method of claim 56.

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70. (New) A method for determining a response profile for a stimulus comprising:

- (a) detecting physical signals from a plurality of units ordered in a probe matrix by contacting the probe matrix with gene transcripts or cDNA derived from said living thing subjected to said stimulus, wherein each unit of the probe matrix confines a probe comprising a different pre-determined sequence of nucleotides, and wherein said sequence is hybridizable with an identified gene of said living thing, or with a transcript of the gene, or with cDNA derived from the gene,
- (b) transducing the physical signals into electrical output signals,
- (c) storing in digital form each electrical output signal in a stimulus response data structure, wherein each stored digital signal is associated (i) with said stimulus and (ii) with the identity of said identified gene, and
- (d) determining a response profile for the stimulus by comparing the stimulus response data structure with a basal response data structure produced by carrying out the steps of detecting, transducing, and storing as above except that the probe matrix contacted with gene transcripts or cDNA derived from said living thing subjected to basal conditions.

71. (New) The method of claim 70 wherein the step of comparing comprises subtracting the elements of the stimulus response data structure and the basal response data structure.

72. (New) The method of claim 70 wherein the step of comparing comprises dividing the elements of the stimulus response data structure and the basal response data structure.

73. (New) The method of claim 70 wherein the probes are 24-240 nucleotides in length.

74. (New) The method of claim 70 wherein the probes comprise lengths of nucleotide sequences selected so as to be hybridizable with a transcript or cDNA derived from a identified gene.

75. (New) The method of claim 70 wherein the probes comprise polynucleotide sequences not hybridizable to more than one contiguous gene of the living thing.

76. (New) The method of claim 70 wherein the gene transcripts or cDNA derived from the living thing are labeled.

77. (New) The method of claim 70 wherein the ordered units in a probe matrix comprise an ordered array of units identified by X and Y coordinates, and wherein output signal data structures comprise matrices with elements identified by the X and Y coordinates.

78. (New) The method of claim 70 wherein the step of storing further comprises storing each digital signal in a computer readable memory.

79. (New) The method of claim 70 wherein the probe matrix comprises oligonucleotide probes that are arrayed on a substrate.

80. (New) The method of claim 70 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 0.5% of the genes of said living thing, or with transcripts of at least 0.5% of said genes, or with the cDNA derived from at least 0.5% of said genes.

81. (New) The method of claim 80 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 5% of the genes of said living thing, or with transcripts of at least 5% of said genes, or with the cDNA derived from at least 5% of said genes.

82. (New) The method of claim 81 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 50% of the genes of said living thing, or with transcripts of at least 50% of said genes, or with the cDNA derived from at least 50% of said genes.

83. (New) The method of claim 80, 81 or 82 wherein the living thing is a human.

84. (New) The method of claim 80, 81 or 82 wherein the living thing is a fungus.

85. (New) The method of claim 80, 81 or 82 wherein the living thing is a eukaryote.

REMARKS

Please enter the foregoing amendment to the specification and claim amendments before examining the application.

Respectfully submitted,

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